OTS: 60-11,832

JPRS: 2935

15 August 1960

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- USSR -

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Distributed by:

OFFICE OF TECHNICAL SERVICES
U. S. DEPARTMENT OF COMMERCE
WASHINGTON 25, D. C.

[redacted]

U. S. JOINT PUBLICATIONS RESEARCH SERVICE
205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

JPRS: 2935

CSO: 3850-N

THE FUNCTIONS OF THE RETICULAR FORMATION OF THE BRAIN STEM

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[Following is the translation of an article by A. M. Ivanitskiy in Patolog. Fiziol. i Eksper. Terapiya (Pathological Physiology and Experimental Therapy), Vol. IV, No. 1, 1960, pages 76-83.]

For a long time the science of the brain proceeded along the route of describing the various centers associated with various peripheral activities in the nervous system. The vigorous development of this science, associated primarily with the name of I. P. Pavlov, led to the idea of cerebral activity as a single whole. This posed research workers with new problems on the study of the interaction of the various brain centers in its intact, integrative activity. The new problems led to new discoveries. About 10 years ago it was found that there are centers in the central nervous system which do not participate directly in the regulation of the somatic or vegetative functions of the body. Their role consists in the regulation of the tone of the other brain centers and in maintaining it at the level optimum for the given moment. Among these centers is the reticular formation (RF) of the brain stem.

The RF consists of a system of nerve cells in the form of a tract which passes through the spinal cord, medulla, hind-brain, mid-brain and inter-brain. The study of the development of the RF shows that it is a derivative of the diencephalon or visceral plate of the medullary tube, from which the cells of the vegetative nervous system also develop (32). The RF was described as an independent system for the first time by Lenhossek (63). Deiters (48) proposed the name "reticular formation", directing

attention to the fact that the combination of the cells in the RF resembles a net.

Many works have been devoted to the morphology of the RF among which we should like to mention the investigations of V. M. Bekhterev (7), who described a number of nuclei and conducting tracts which belong to the reticular formation. Recently, the works of Olszewski (76, 77) and other authors (3, 11, 12, 16, 17, 44, 45, 75) have been devoted to this problem. As a result of these and the large number of other works it has been established that the RF is not a diffuse formation from the morphological point of view but rather consists of a large number of nuclei of various structures which are closely connected with one another by a profusion of fibers in a network which go in different directions (Figure 1). The cellular composition of the RF is exceptionally varied. The majority of cells has a short axon; however, cells with long ascending axons have also been described (45).

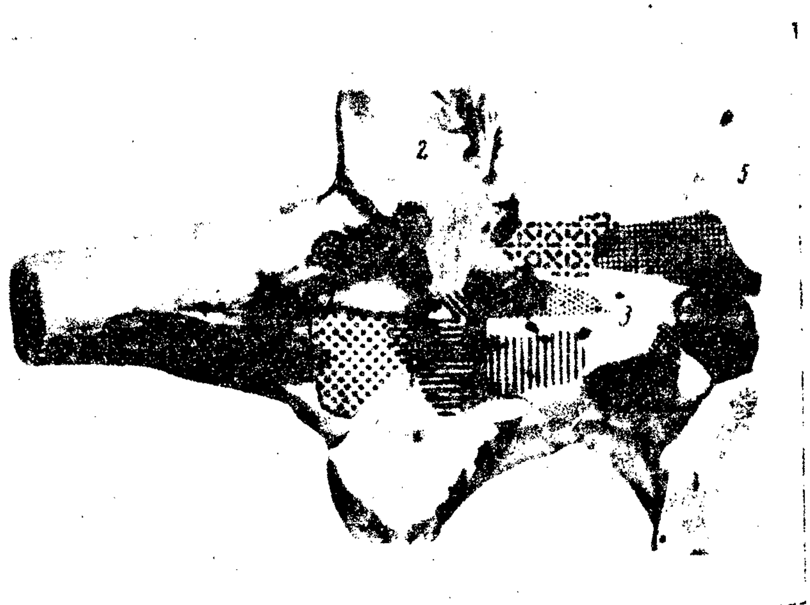

Figure 1. Horizontal Projection of Some Nuclei of the RF of the Human Brain Stem. 1 -- Rhomboid fossa; 2 -- cerebellar peduncles; 3 -- corpora quadrigemina; 4 -- epiphysis; 5 -- thalamus (76).

It has been established by physiological

investigations that the RF exerts a regulatory influence on the following nervous structures: 1) the higher cerebral centers and particularly the cerebral cortex; 2) the centers of the hypothalamic area and medulla, including the respiratory and vasomotor centers; 3) the spinal cord centers; 4) the afferent neurons.

In this article the principal attention was given to the effects of RF on the more proximal centers of the nervous system, because this subject is of the greatest interest and has been worked out most completely. These influences, and chiefly the effect on the electrical activity of the cerebral cortex, underlay the conception of the ascending activating reticular system formulated by Magoun and Moruzzi (66, 67, 72, 74).

In these works the authors started with the experiments of Bremer (41), establishing the fact that transection of the brain at the level of the first cervical vertebra (encephale isolé preparation) does not exert any considerable influence on the electrical activity of the higher centers (electroencephalogram). After the effect of a number of external stimuli changes were observed in the electroencephalogram characteristic of a transition from sleep to waking. These changes were afterwards designated the "arousal reaction". They consisted of the disappearance of the high-voltage slow rhythms and a replacement of them with low-amplitude fast waves and are usually accompanied by corresponding changes in the external behavior of the animal.

In contrast to this transection of the brain at the level of the posterior colliculi (cerveau isolé preparation) immediately leads to the animal's "falling asleep" with typical changes in the electroencephalogram. The effect of external stimuli is ineffective at this point.

Magoun and Moruzzi deserve the credit for establishing the importance of the functions of the RF of the brain stem for transitions from sleep and waking. The data which they obtained amounted to the following.

1) Transection of the classic conducting tracts with preservation of the RF of the brain stem does not result in the animals going to sleep.

2) Isolated destruction of the RF with preservation of the conducting pathways produces changes in the electroencephalogram which are characteristic of sleep.

3) Direct stimulation of the RF during sleep or light anesthesia leads to waking.

4) On waking the electroencephalogram reaction is of a generalized nature and is not limited to simply the site of projection of these stimuli in the cortex. The arousal reaction is observed also after the extirpation of those areas of the cortex in which the given stimulus is directly projected.

5) Activation of the electroencephalogram may be noted also in the absence of any afferent impulses, for example, after attempts to look into darkness.

An analysis of these data led to the idea of the existence of special centers in the brain the task of which is the maintenance and regulation of the tone of higher nerve structures. These centers, which are located in the RF of the brain stem, were designated the "ascending activating reticular system" (Figure 2).

Figure 2. Schematic Representation of the Ascending Activating System. The system receives collaterals from the long conducting pathways and exerts a diffuse influence on the tone of the higher centers.
1 -- Medulla; 2 -- pons; 3 -- corpora quadrigemina; 4 -- thalamus; 5 -- hypothalamic area; 6 -- hypophysis; 7 -- corpus callosum (67).

The tone of the activating system itself depends on several factors. The principal ones of them are the impulses arriving at the RF cells along the collaterals from the long afferent and efferent conducting pathways passing through the area of the medulla and mid-brain (70, 84). Here, the impulses from the nuclei of the trigeminal nerve are of special importance (73, 80). It should be noted that stimulation of the endings of this nerve, for example, with cold or by smelling ammonia, has for a long time been used for bringing patients out of a syncopal state. Aside from the exteroceptive influences interoceptive stimuli, particularly impulses from the carotid area (40), participate in regulating the tone of the reticular system. Certain reticular elements apparently possess an automatic activity also, that is, they are capable of maintaining their excitation even without an influx of external stimulation, but automatic activity alone is inadequate for maintaining the waking state.

Finally, an important part in the regulation of the reticular system tone is played by influences from the higher centers: the olfactory portion of the brain, cerebellum and particularly of the cerebral cortex.

The effect of the cerebral cortex on the RF function was first shown in the experiments of Bremer and Terzuolo (43) and has been confirmed by other investigators (36. 37). These influences may be both of a facilitative and of an inhibitory nature. The existence of cortical influences at the activity level of the reticular system makes it possible to draw the conclusion of the existence of a cortical-reticular-cortical mechanism by means of which the most effective regulation of the cerebral cortical tone is achieved, that is, the establishment of the optimum level of its activity as applied to the problems of the given moment (73).

Aside from the neural influences the RF tone depends also on a number of humoral factors, which will be described in detail below.

An important characteristic feature of the RF is the extensive generalization of excitation within this structure. This is associated with the characteristics of the histological structure and functional properties of the nerve cells of the RF. In experiments with tapping potentials from solitary RF neurons it has been shown that the change in the frequency of discharges of the same cell may be caused by the application of different peripheral

stimuli, for example, visual, auditory, tactile and olfactory, as well as by stimulation of other brain centers (cerebellum, cerebral cortex) (34, 37, 69, 84).

Undoubtedly, such an extensive irradiation of excitation along the reticular system contributes to the maintenance of its active state even with a comparatively small number of stimuli. However, this convergence of impulses onto a solitary neuron is, to a certain degree, limited, because each nerve cell reacts to several but not to all types of stimulation (83). With the effect of weaker stimuli it is possible to establish even a certain spatial localization of the stimuli within the RF; however, with stronger stimulation an extensive irradiation of the excitation is observed throughout the entire system.

The ascending influences from the RF of the brain stem spread along the so-called "nonspecific conducting pathways", along which, in contrast to the classic specific conducting pathways, no specific information is transmitted concerning the state of the external or internal milieu, but rather only a general and generalized effect is exerted on the tone of the higher centers.

For the purpose of explaining the activating or, as some say, "energy" role of the RF the cerebral cortex may be compared with the screen of a television tube. The stimulation which comes into the cortex along specific conducting pathways will contribute to the specific content of the television image, but the influence exerted by the RF can be likened to the effect of a system regulating the brightness and contrast of the image. Here, the transmission of the biologically most important information will be associated with an increase in the brightness and contrast of the image. However, it should be kept in mind that this comparison has been made here only for greater clarity and does not reflect the true nature of the processes in the brain.

The morphological indications of the presence of nonspecific conducting pathways were first obtained by Lorente de No (65). As is well known, the specific tracts go to the cortex from the sensory nuclei of the thalamus and end in the cells of the IV layer of the cortex. In contrast to this the nonspecific tracts begin from the reticular nuclei of the thalamus and terminate in the cells of all the layers of the cortex. According to the data of Chang (33, 47) and Bremer (42), the nonspecific fibers form numerous synapses in the superficial cortical layers

with the dendrites of the cortical cells. By means of these synapses they can exert a facilitating or inhibitory influence on the excitability of cortical neurons and change their reaction to impulses passing along specific pathways.

The result of excitation of the reticular centers is the activation of the electroencephalogram (depression of slow and the appearance of fast waves). Tapping the potentials from solitary cells made it possible to establish the fact that this reaction is accompanied by an increase in the frequency of discharges of the cortical neurons (50) as well as by the development of a prolonged electronegativity in the cerebral cortex (35). According to the data of V. S. Rusinov (29), the development of slow negative potentials in the cortex is associated with an increase in its excitability and is of great importance in elaborating conditioned reflexes.

Along with RF of the hind- and mid-brain, which play an important part in the maintenance of the waking state, a nonspecific system of the thalamus has been described, to which the paraventricular nucleus, the interlaminar nucleus, the zona reticularis and the centrum medianum. This system also exerts diffuse influences on the cortical activity. In the experiments of Morison and Dempsey (71) it has been shown that stimulation of the interlaminar nuclei of the thalamus at a rhythm of three to 15 seconds produces a series of negative potentials of gradually increasing amplitude in the cortex. This reaction is designated a "recruiting reaction" by the authors. It has been investigated in greater detail in the experiments of Jasper and his coworkers (57-61) as well as in the works of S. P. Narikashvili (21, 22). The "recruiting reaction" is somewhat more limited in a spatial respect than the arousal reaction, and its diffusion and nature depend to a certain degree on the localization of the stimulus. In Jasper's opinion, the thalamic RF is of great importance in the distribution of the excitability level between the various cortical areas. The thalamic reticular system also plays a definite part in the origin of the cortical rhythm, particularly the alpha-rhythm. Roytbak (27) believes that the nonspecific thalamic nuclei have a substantial influence on the elaboration of inhibitory reactions, whereas the RF of the mid-brain exerts its influence in the elaboration of positive reflexes.

It should be noted that the idea of the diffuseness, "nonspecificity" influences exerted by the RF are being subjected to criticism on a progressively greater scale at the

present time. Olszewski wrote that the very term "RF" will become unnecessary in the future by virtue of the development of exact knowledge concerning the functions of each of the nuclei of the reticular formation (76). A definite step in this direction was made in the work of Brodal (44), where the author compares the data concerning the function of the RF and its anatomic structure. Apparently, in a number of cases definite correlations can be established between the localization of functions and the characteristics of the anatomic structure of the reticular system. Similar data have been presented also by S. P. Narikashvili (22). Moruzzi has shown that one of the most important functions of the reticular system, maintenance of the waking state of the cortex, depends chiefly on centers located at the boundary of the tectum of the pons and mid-brain (presented at the Colloquium on Electroencephalography of Higher Nervous Activity, Moscow, 1958). The different localizations of the afferent systems within the RF have been mentioned above.

Therefore, we may draw the conclusion that the RF reacts like a more or less diffuse system only after the effect of strong, for example, painful stimulation. Under ordinary conditions it is possible to determine a distinct spatial localization within this system, although the degree of functional overlapping in it is considerably greater than in the specific system (20).

P. K. Anokhin (4, 5, 6) is developing an original viewpoint of the RF function. He advanced the idea of the dependence of the form of activation of the cortex on the biological importance of various kinds of activity for the organism. Thus, activation from a biologically negative, for example, defense, activity is associated with excitation of different RF structures from those excited from food activity. The pharmacological characterization of these structures is also different. Thus, the injection of adrenalin (see below) increases the excitability of the structures associated with the defense activity, while thorazine, on the other hand, eliminates the activation reaction caused by defensive stimulation without exerting any influence on the food activity or even increasing it. Here, typical changes are observed not only in the electroencephalogram but also in the external behavior of the animals.

From the general pathological and practical points of view data concerning the intimate relationship between the functions of the RF and the sympathico-adrenal system are interesting. It has been established through the investi-

gations of Bonvallet, Dell, Hiebel and Hugelin (38-40, 49) that the intravenous injection of very small doses (of the order of several γ/kilograms) of adrenalin produces a typical arousal reaction in the cerebral cortex. This reaction, however, does not occur if a cerebral transection has been performed in the animals at the level of the corpora quadrigemina. The typical effect of adrenalin is lacking also after the selective injury of the RF, which speaks for its direct effect on the cells of the RF (81, 82).

Biochemical examination of the brain (85) showed the existence of areas with a high concentration of adrenalin or noradrenalin in the brain stem. The topography of these areas is in good agreement with the localization of the reticular structures which are related to maintaining the waking state. Apparently, the synapses, at least part of the nerve cells included in these structures, are of an adrenergic nature, which explains their high degree of sensitivity to adrenalin.

Data concerning the sensitivity of the reticular formation to adrenalin, undoubtedly, should be utilized also in the analysis of the mechanism of emotional reactions described by Cannon (46). It should be noted that the idea of the close connection of the reticular and sympathetic systems serves to develop L. A. Orbeli's conception (24) of the adaptive-trophic role of the sympathetic nervous system (13, 14).

In addition to the adrenal system the RF is associated also with certain other hormones. Thus, hydrocortisone and corticosterone exert a regulatory influence on the function of the ascending activating system (18).

Data concerning the ascending influence of RF have been a great contribution to science. It should be noted that the problem of the role of the subcortical structures in the higher nervous activity was posed in the classic works of I. P. Pavlov (25). The idea of the "blind strength" of the subcortex and its influence of its tone on the level of conditioned-reflex activity cannot be in better agreement with the nature of the influences exerted on the cortex by the activating system. In a number of works performed by the conditioned-reflex method, it has been shown that the strength of the unconditioned stimulus, on which the tone of the subcortex depends, directly influences the strength and working capacity of cortical cells (2, 15). Based on this, the study of the functions of the RF should be regarded as a further development and concretization of these

views by I. P. Pavlov; its development is particularly valuable because it is associated with the application of new investigational methods, such as electrophysiological methods. It is interesting that the development of the science of the brain, including also the functions of the RF stimulated the interest of foreign investigators in the teaching of I. P. Pavlov (31). This is associated with the fact that only the study of conditioned reflexes makes it possible to understand the biological meaning of cerebral reactions to various external influences. The problem of the role of the reticular structures in the conditioned-reflex activity is one of the most important ones in modern neurophysiology; however, the great majority of investigators, including those abroad, recognizes that the cortex has the leading role in carrying out the conditioned reflex as an integral adaptive act.

The idea of the cerebral cortex as the highest level of analysis and synthesis of stimulation is being confirmed also in the data of comparative anatomy (32). These data constitute evidence to the effect that during the course of phylogeny a progressive development occurs of the fore-brain and particularly of the cerebral cortex. The RF, on the other hand, is developed in the lower vertebrates to a greater degree than in the higher degree.

Attempts at creating a theory relegating the main role in carrying out the function of consciousness to a non-specific system (theory of the centrencephalic system) (78) has not been widely recognized by the majority of research workers.

The connection of the RF with the respiratory and vasomotor centers has been studied comparatively little, although this problem is of great practical interest. Strictly speaking, these centers represent parts of the RF itself, which have become specialized during the course of phylogeny into independent functional entities. Therefore, a change in the tone of the RF frequently produces corresponding changes in these centers because of the irradiation of excitation or inhibition. As an example of such influences mention may be made of a hyperpnea from muscular activity. In this case, the tone of the reticular neurons is increased because of the influx of impulses to them along the collaterals of the pyramidal tracts. Subsequent irradiation of the excitation to the respiratory center leads to an increase in the depth and frequency of respiration (28). The differences between respiration during sleep and respiration during waking are generally known also. In its turn,

irradiation of excitation from the respiratory center to the reticular system can alter both of the tone of this system itself and the tone of higher and lower centers.

The relationships of the RF with the vasomotor center to a certain degree are similar to those which have been described through the respiratory center. For example, it has been shown that the reaction of activation of the cortex is usually accompanied by an increase in the blood pressure (39). This effect may be produced both by the influence of external stimulation and by the direct stimulation of the medial centers of the RF of the mid-brain. The reverse relationship can also be observed. Thus, when there is a reflex depression of the vasomotor center, which is produced by stimulation of the pressor receptors of the carotid sinus, a reduction in the tone of the reticular system is observed. The sensitivity of the RF to adrenalin should also be kept in mind in analyzing the problem of the complex interrelationship between the vasomotor and reticular centers.

There are data in existence also concerning the interrelationship of the RF with the area of the hypothalamus, which plays an important part in combining the vegetative and humoral regulatory reactions of the body (10, 55).

The influence of the RF on the reflex activity of the spinal cord may be of either a facilitating or an inhibitory nature. They spread in response to physical (68, 79) and tonic (53) reflexes. It is believed (64) that impulses from the reticular system prepare the spinal motor neurons for the reception of slower spreading impulses which go along the pyramidal tracts. An influence of such a nature was detected for the first time in the classic experiments of I. M. Sechënov (30) on central inhibition, although they were not tied in at that time with stimulation of the RF. The regulation of the spinal tone by the cerebral cortex and cerebellum are also apparently accomplished by neurons of the reticular formation. At the present time, it may be considered proved that the descending reticular system is anatomically an independent structure, and is not part of the same whole as the ascending system.

The influence of the RF on the excitability of afferent neurons has been shown in the experiments of a number of research workers. The reticular formation regulates the excitability of retinal elements and of muscle spindles (52) of the nerve cells of the cochlear ganglion (9, 62). The idea has been expressed that these influences

are connected with the inhibition of sensory neurons which are outside the sphere of attention. The mechanism of this regulation has not been adequately studied as yet.

The study of the functions of the RF of the brain stem is of great importance not only for physiology but also for clinical practice, because the disturbance in the regulatory influences of this formation with respect to higher and lower centers can lead to a pathological alteration of their function.

The involvement of the ascending activating system leads to the impairment of the regular alternation of sleep and waking, which has been observed both in experiments on animals and in people with pathological processes in the area of the brain stem (tumors, encephalitis, trauma) (66). A considerable destruction of this system is a threat to life. French (31) described several cases of traumatic injury of the RF. All the patients were unconscious for several months after the trauma and until the time of death.

The involvement of the activating system is frequently observed also in the so-called diencephalic syndrome (10). In these patients, along with deep-seated disturbances of the vegetative functions changes in the electroencephalogram have also been described attesting to the pathological increase or, on the other hand, a reduction in the tone of the reticular system.

Undoubtedly, however, the pathology of the reticular system is not exhausted by cases of gross organic involvement of the brain stem area. Persistent insomnia, increased nervous excitability or, on the other hand, apathy in many cases are apparently associated with the functional abnormalities of the reticular system, which are the result of its overstrain or toxic influences in the past. From this point of view the data of Lishak, who showed the great part of the reticular formation in the pathogenesis of experimental neuroses, are interesting (reported at the Ninth Congress of the All-Union Society of Physiologists, Biochemists and Pharmacologists, Minsk, 1959). Here, a disturbance of the regulatory influences of the suprarenal hormones are also of definite importance with respect to the RF, which permits us to pose the question of pathogenetic therapy of these disturbances. These data, as well as the indication of the close connection between RF and the hypothalamic area indicate the important part of the nonspecific system in the nerve mechanisms of "stress" (10).

Further study of the effect of the reticular formation on the medullary centers and, particularly, on the vasometer center are also very important, apparently, from the viewpoint of pathology. In any case, the effectiveness of certain methods of treating hypertensive states by means of preparations acting on the reticular area should attract the attention of pathologists to this problem.

The disturbance in the functions of the RF exerts an influence also on the development of certain gastrointestinal diseases (23).

The great importance of disturbances in the functions of the reticular system in the pathogenesis of many diseases should be taken into consideration in developing methods of treatment. The perspectives which opened up in this direction are quite favorable. This is associated with the fact that cells of the reticular system possess a high degree of susceptibility to various humoral influences, which is apparently accounted for by the characteristics of their biochemical and synaptic organization. Therefore, the pharmacology of the reticular formation even now includes a number of effective drugs. This problem is of independent interest. In the present article we can present it only in a conspective form (see the review works devoted to this problem, 8, 26, 55, 86).

It has been shown that the effect of various anesthetic agents (ether), barbiturates (luminal) and analgesics (morphine) is accomplished to a considerable degree through the reticular system. Cholinergic substances are highly active with respect to the RF, and by means of them it is possible to produce both an increase (ephedrine) and a decrease (atropine, scopolamin) in the RF tone. Mention has already been made of the effect of adrenalin on the reticular system. The mechanism of action of amphetamine is also explained, by certain authors, by its influence on the adrenalin-sensitive components of the RF.

Finally, the effect from the application of a large group of ganglion-blocking and neuroplegic agents is also, to a considerable degree, associated with their effect on the RF. As is well known, the use of these preparations is effective in the treatment of a number of somatic and mental diseases as well as in surgical practice in artificial hibernation and controlled hypotension. The effect of some of these preparations, particularly thorazine, on the reticular system has been studied in detail (1, 18, 19, 54). It possesses adrenolytic properties, and its effect is

associated with the influence on the adrenergic components of the RF. The mechanism of action of certain other preparations (reserpine) has not yet been adequately studied.

In appraising the contribution made by the study of the functions of the RF to our ideas of the operation of the brain, we must recognize it as useful from many points of view. In regarding the perspectives of its development, we see that the majority of the problems posed by the study of it are still far from being conclusively solved. Their further development is of great theoretical and practical importance.

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Received 22 July 1959

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